Universidade de Aveiro Secção Autónoma de Ciências da Saúde
Ano 2015

TATIANA RIBEIRO FAUSTINO

RELATÓRIO DE ESTÁGIO NA DIREÇÃO DE PRODUTOS DE SAÚDE

CURRICULAR TRAINING REPORT AT "*DIREÇÃO DE PRODUTOS DE SAÚDE*"

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Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica realizado sob a orientação científica da Dra. Judite Neves, Diretora da Direção de Produtos de Saúde e do Professor Doutor Bruno Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

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palavras-chave Dispositivos Médicos, INFARMED, Regulamentação, Avaliação de Conformidade, Requisitos Essenciais, Marcação CE

Resumo

O objetivo deste relatório é descrever a minha experiência durante o estágio decorrido no INFARMED, I.P., no Departamento de Produtos de Saúde no âmbito do Mestrado em Biomedicina Farmacêutica.

O relatório é dividido por uma parte inicial na qual faço um enquadramento geral relativo aos dispositivos médicos, o que são, como são qualificados/classificados, como são regulados atualmente e o que está proposto para alteração. Depois faço uma descrição das tarefas que realizei e finalmente uma discussão dos pontos chaves dessas tarefas.

Keywords Medical Devices, INFARMED, Regulation, Conformaty Assessment, Essential Requirements, CE Marking

Abstract

The purpose of this report is to describe my experience in internship elapsed at INFARMED, I.P. in the Department of Health Products in the scope of the Master's degree in Pharmaceutical Medicine.

The report is divided into an initial part where I make a general framework of the medical devices, what they are, how they are qualified/classified, how they are currently regulated and what is proposed to change. Next, I do a description of the tasks I performed and finally a discussion of the key points of these tasks.

Abbreviations

AIMDD	**Active Implantable Medical Devices Directive**
CA	**Competent Authority**
CE	**"Conformité Européene"**
CFS	**Certificate of Free Sale**
COEN	**Compliance and Enforcement Group**
DoC	**Declaration of Conformity**
DAM	**"*Direção de Avaliação de Medicamentos*"**
DPS	**"*Direção Produtos de Saúde*"**
EU	**European Union**
EEA	**European Economic Area**
EFTA	**The European Free Trade Association**
FABDM	**Manufacturers' platform**
GMDN	**Global Medical Device Nomenclature**
HTA	**Health Technology Assessment Systems**
IVD	***In Vitro* Diagnostic Medical Device**
IVDD	***In Vitro* Diagnostic Directive**
MD	**Medical Device**
MDD	**Medical Devices Directive**
MDSS	**Medical Device Systems and Sets**
NCA	**National Competent Authority**
NHS	**National Health Systems**
NB	**Notified Body**
QAS	**Quality Assurance System**
SOP	**Standard Operating Procedures**
SDIV	**Distributors' platform**

Table of contents

Index of Figures

Index of Tables

1. Introduction

This report is performed within the scope of a curricular internship of the Master´s Degree in Pharmaceutical Medicine. My internship occurred at Infarmed – National Authority of Medicines and Health Products, I.P. from November 2013 to October 2014. During the first seven months I was in the medical devices evaluation department the "*Direção de Produtos de Saúde"*(DPS) and following four months I moved to the medicines evaluation department "*Direção de Avaliação de Medicamentos*" (DAM). The initial program included solely the training in DPS, however during the internship there was the opportunity to training also in DAM. The experience passed in DAM will not be the focus of this report, so I will just describe my experience in DPS and I will do a critical appraisal and specify the principal problems that I found in the different tasks I have been assigned.

I applied to do this internship because I wanted to gain experience in an area different from my previous professional experience. The internship in the Competent Authority (CA) was the opportunity I was looking for.

1.1. Objectives

The main goal of this internship was to obtain a global vision of Medical Devices' regulation and to know how the CA supervises the market. For this, the following specific objectives have to be achieved:

- Qualify and classify Medical Devices (MD)
- Know the current legislation (National and European) and Guidelines applicable to MD
- Collaborate in the process of the formal conformity assessment of MDs
- Work with the CA manufacturer's platform (FABDM) and distributor's platform (SDIV)
- Use the tools and mechanisms established under the European cooperation for market surveillance: prepare and develop the Compliance and Enforcement Group (COEN) and enquiries
- Know and comply with the quality management system of the institution including the manual and Standard Operating Procedures (SOPs).

Apart these goals specifically related to the MDs environmental the internship was also the purpose improve and give new a soft skills as:

- Communication skills (written and verbal)
- Time management

- Being a team player
- Organizational skills
- Sense of responsibility
- Critical sense
- Diligence

1.2. Host Institution

INFARMED – National Authority of Medicines and Health Products, IP hereafter designated as INFARMED is a governmental agency accountable to the Health Ministry. Its purpose is to monitor, assess and regulate all activities relating to human medicines and health products for the protection of Public Health. So, it is INFARMED´s competence, to license, certify, authorize and approve entities, activities and procedures. The mission of this institution is supervising the sectors of human medicines and health products and ensuring the access of health professionals and citizens to quality drugs and health products, effective and safe.

INFARMED as stated in activity plan for year 2014 assumes an important role in European and International context in addressing emergent challenges as strengthening competitiveness in the pharmaceutical sector, fast technological advance, the growing demand in terms of transparency, effective combating of falsification and counterfeiting (1).

INFARMED is divided into several units according to the follow organizational chart:

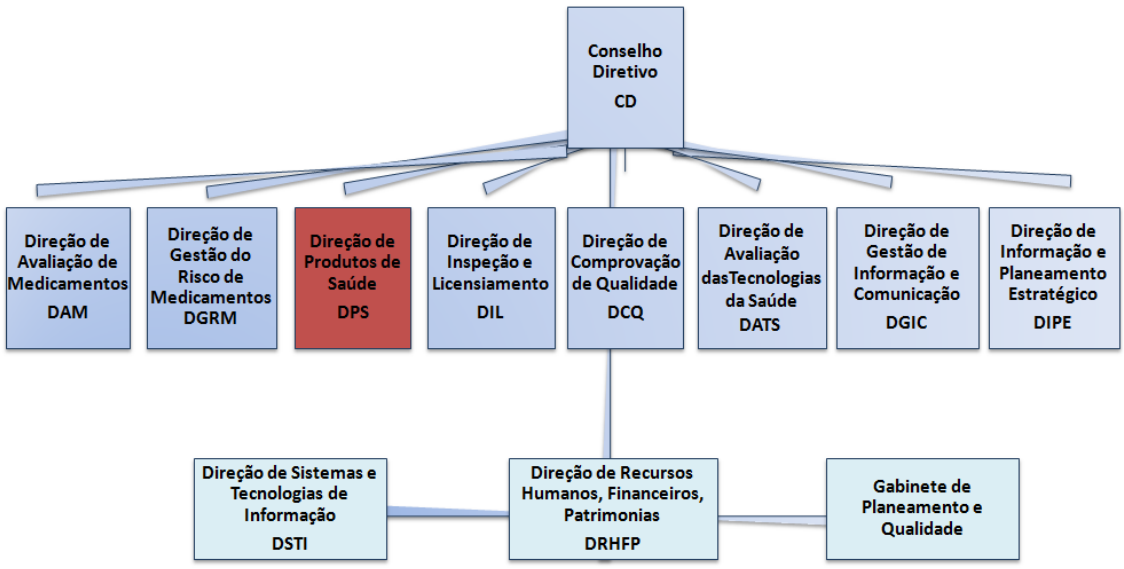

Figure 1 – Organizational chart of structure and organization of INFARMED, IP (2)

1.2.1. "*Direção de Produtos de Saúde*"

The DPS is one of the basic units of INFARMED that includes the areas of MDs, cosmetics and Personal Care Products. Additionally, this department has a subunit of vigilance, the "*Unidade de Vigilância de Produtos de Saúde"*. The DPS has the mission of regulation, market surveillance and vigilance of health products encompassing the clinical investigation of MD according to the highest standards of protection of public health. DPS participates in the responsibility of ensuring that healthcare professionals and citizens in general have access to health products that comply with applicable regulatory requirements (2). The DPS consists in a multidisciplinary team composed by professionals from various areas of health and technology including pharmacists, engineers, veterinaries, biologists and radiographers. Taking into account the great diversity of MD products, a multifaceted team like this is undoubtedly of high value for the operation of this department.

1.3. State of the art

1.3.1. Medical Devices Market

The MDs industry is a complex and diverse area considering that the term "medical device" covers a vast range of equipment, from syringes and band aids to pacemakers and breast implant. It constitutes a key sector for healthcare and it is one of the most innovative sectors, improving and saving lives by providing innovative solutions for diagnosis, prevention and treatments (3, 4).

The social and political changes during the last years namely ageing population, economic global recession, increasing of patient expectations about health care and access to innovative products are the current issues that MD´s market and Governments have to deal. Due to this crisis, the budgets of National Health Systems (NHS) are constrained, threatening the reimbursements and reducing the reimbursements' rates which, ultimately, affect the development and competitiveness of the MDs´ Industries. Thus, the Governments and their National Competent Authorities (NCA) have to deal with the increasing needs of citizens and, at the same time, with the scarce economic resources (3, 5).

The international regulatory harmonization and its coordination is recognized by all MD´s stakeholders as a crucial measure for improving the confidence in the European system not only within the European Union (EU) but also outside of it.

The measurement of the value of the MDs through the Health Technology Assessment Systems (HTA) is an important tool used by the decision makers to control the scarce resources. However, it is important be aware that this tool should not be used only as a way of cost-containment but should be used to assess the real value/ effectiveness of the MD in the context of the citizen's needs. It is necessary to create guidelines for good HTA practices, develop standardised practices, predictable and common criteria for HTA methods and designed specifically for MDs. Industry needs to provide products that increase efficiency and reduce the costs. For instance, MDs that facilitate minimally invasive surgery that allow faster recuperation of patients and also increase the number of operations performed per day of surgery (6).

1.3.2. Medical Devices Regulatory Environment

Taking into account that my internship was performed in the Portuguese CA, in this report I will refer only to the law applicable in the EU.

The MD regulation began in the United States of America, the US Medical Device Amendments, in 1976 under the responsibility of the Food and Drugs Administration. After this, MDs were defined and the risk-based classification was introduced and the regulatory process for each class was outlined. In Europe, the first MDs regulation was outlined only in the '90s, with the introduction of one of the most important directives, the Directive 93/42/EEC (7).

The regulatory framework for the MDs in European Union is based on three directives:

- Directive 90/385/EEC – Active Implantable Medical Devices Directive (AIMDD)
- Directive 93/42/EEC - Medical Devices Directive (MDD)
- Directive 98/79/EC – In Vitro Diagnostic Directive (IVDD)

All these directives are based on the "New Approach" and aim to ensure the functioning of the internal market as well as a high level of protection to human health and its safety. The "new approach" means that the legislation specifies only the essential requirements that are general and mandatory and the detailed technical specifications used to demonstrate conformity with the essential requirements are according to the voluntary harmonized standards (8, 9). MDs are not subject to a pre-market authorisation by a regulatory authority but only to a conformity assessment which, for medium and high risk devices, involves an independent third party, a so-called "Notified Body" (NB). Once certified, devices bear the CE marking which allows them to circulate freely in the EU/EFTA countries and Turkey.

These directives have been reviewed and updated over time by the introduction of several directives, including the last technical revision triggered by Directive 2007/47/EC amending the AIMDD and MDD. This directive also amends Directive 98/8/EC which concerns the placing of biocidal products on the market (10).

According to the MDD, all MDs have to fulfill with the essential requirements stated in this directive before being placed on the market. These requirements cover the MDs themselves and the materials they are made of and the tests they must pass, including standards on clinical investigations. The compliance with these essential requirements serves as a mechanism for proof that the MD complies with its intended purpose and it is safe. The European NCAs rely upon the fulfillment of these requirements to certify the formal compliance of devices placed on the market (9, 11, 12).

1.3.3. Classification of MD

To classify MDs, it is necessary to be aware that it is framed in the definition of MD. According to the MDD, a MD is any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,
- and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means (13).

The classification of MDs is a 'risk based' system that evaluates the potential risks associated to the devices and the vulnerability of human body. They are classified according to a graduated system. It means that in this system the level of control corresponds to the potential danger related to the type of the MD concerned. MDs are classified into classes: I, IIa, IIb and III. The conformity assessment process is also performed according to MDs classification. Thus a class III

MD will have to conform to more rules to prove its effectiveness and harmlessness than an inferior class device.

The classification of MDs is determined according to the duration of use (transient, short term, long term), contact with the body (brain, heart, etc.), degree of invasiveness and the potential risks associated with design and manufacture. The classification rules are described in Annex IX of Directive 93/42/EEC and in MEDDEV 2.4/1 Classification of MD. There are eighteen rules and they are subdivided into four groups (Table 1) (14).

Table 1 – Classification Rules-MD (14)

Rules	Device
Rules 1 – 4	Non-invasive Devices
Rules 5 – 8	Invasive Devices
Rules 9 – 12	Active Devices
Rules 13 –18	Special rules

An active medical device is a device that for its functioning needs on a source of electrical energy or any source of power other than that directly generated by the human body or gravity (13).

The *in Vitro* Diagnostic Medical Devices (IVDs) is a device, whether used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles (15). Similarly to the other MDs, these are classified into four groups, two classes annex II (list A for high-risk devices and list B for medium-risk devices), a self-testing IVD class for devices intended for use directly by lay individuals and a general class with the lower risk (Table 2) (16).

Table 2- IVDs' Classes (16)

Class	Examples
Annex II, list A	reagents including related calibrators and controls for use in HIV, HTLV and hepatitis assays
Annex II, list B	reagents including related calibrators and controls for use in rubella, toxoplasma, cytomegalovirus and chlamydia assays.
Self-test	test kits used in a home environment – pregnancy testing.
General	bacteriological culture media, cell cultures for virus isolation, specimen containers.

1.3.4. CE Marking

CE marking is the MD manufacturer´s claim that a product meets the essential requirements of European Directives and is a legal requirement to place a device in the EU market. It shows that the device is fit for its intended purpose and meets legislation relating to safety (Figure 2).

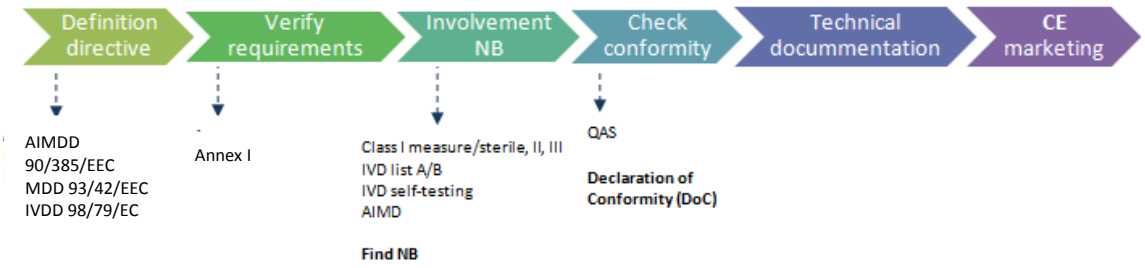

Figure 2– General order of activities in compliance with European regulation (17, 18)

Additional to the CE marking, the manufacture or its authorized representative (i.e) within the European Economic Area (EEA) must sign a Declaration of Conformity (DoC) (Figure 3). The manufacture is the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party and the authorized representative is the person established in the Community who,

explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer [13]. This document also indicates that the product meets all the necessary requirements laid down in the applicable directives (1, 11, 15).

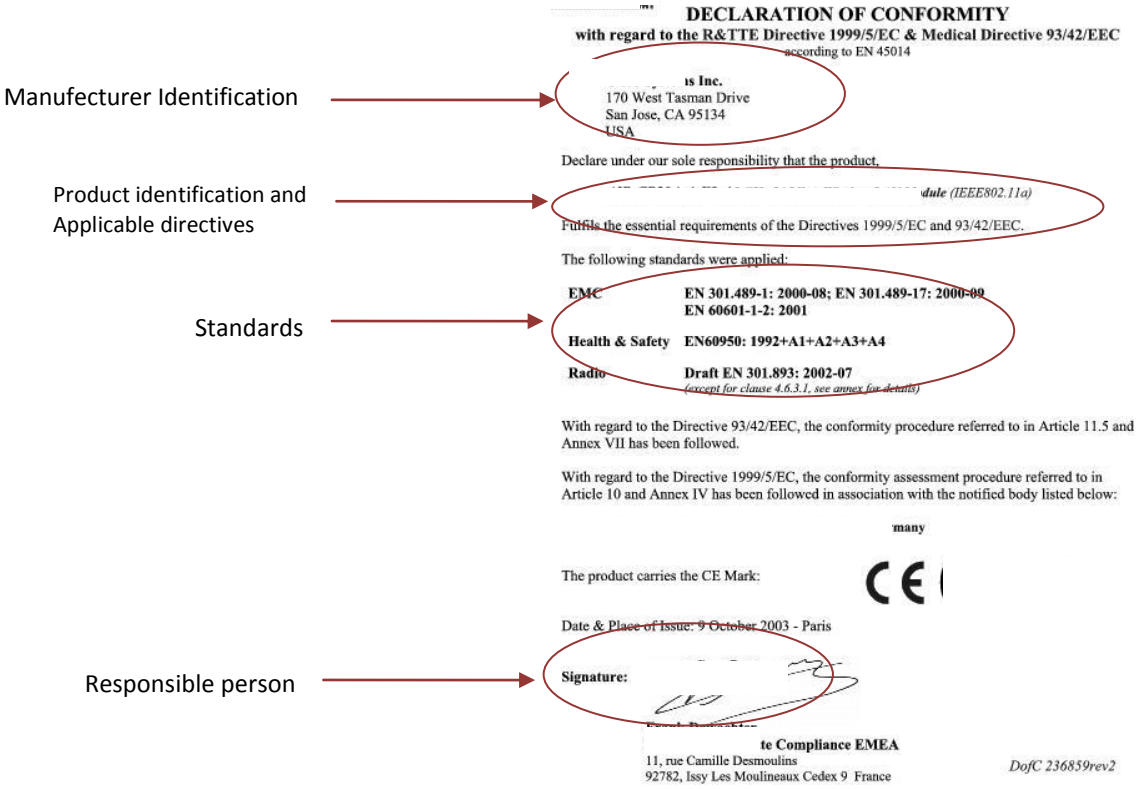

Figure 3 – Example of Declaration of Conformity (19)

For all devices except Class I non-sterile and non-measuring, the manufacturer should also have a Quality Assurance System (QAS) that ensures that MD fully meets the standards defined in the technical documents. The procedures related to this quality assurance are set out in Annex II (full quality assurance) and Annex V (production quality assurance) of MDD. In the technical dossier, the manufacturer displays all data that prove compliance with these requirements including the clinical evaluation and risk assessment. For all classes of devices above class I (including class I sterile or class I with measure functions), the QAS and technical dossier must be audited by a NB, a third party designated by CA to audit MD companies and products. Specifically, for these types of MDs, it is required a CE Marking Certificate for the MD issued by NB.

1.3.5. Notified Bodies

The NBs are third party bodies designated/accredited by CAs to carry out conformity assessments of MDs under the MDs Directives. The assessment usually includes an audit of the manufactures' quality systems and an evaluation of the MD's technical documentation depending on their classification. The manufacturers should choose the NB taking into account their technical competencies and experience.

A list of designated NBs from each Member State per directive and per scope of action is available in Nando's database in the European Commission website (20).

Decisions taken by the NBs in accordance with Annexes II, III, V or VII of MDD shall be valid for a maximum of five years and may be extended on application, made at a time agreed in the contract signed by both Parties, for further periods of a maximum length of five years (21).

The NB issues a CE Certificate which certifies that the product(s) is (are) covered in scope Figure 4.

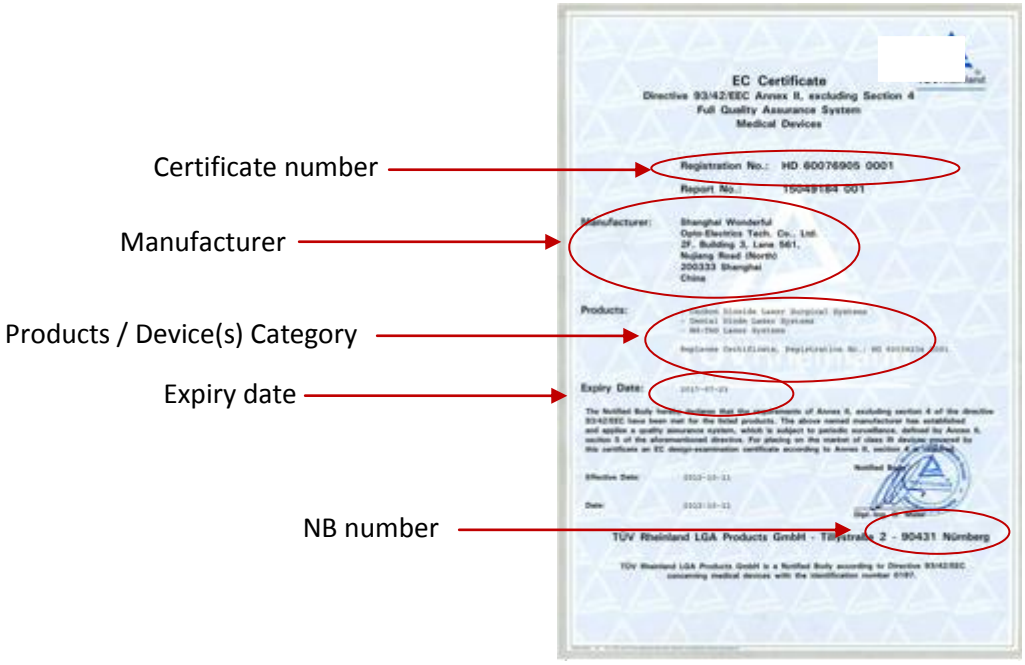

Figure 4 – Certificate–Example of EC (22)

1.3.6. Portuguese Legislation

In Portugal, MDs are regulated by Decree-Law 145/2009 of the 17th of June that transposes the Directive 2007/47/EC into the national law. It establishes the rules regarding investigation, manufacturing, commercialisation, functioning, supervision and advertising of MDs (including active implantable) and respective accessories. Regarding to the IVDs, the Directive 98/79/EC is transposed to the Portuguese law under Decree-Law no. 189/2000 of 12th August (15, 16).

1.3.7. Harmonized and Standards Guidance

The European Harmonized Standards under the EU harmonization legislation are published in the EU Official Journal. These publications are listed harmonized standards that are in place and should be applied for each MD in accordance with the applicable directives (23).The harmonized standards give the presumption of conformity with the Essential Requirements of the applicable directive. The use of the standards is not mandatory. However, if not harmonized standards are used, the manufacturer has to document the alternative solution adopted to fulfill the essential requirements of the directive (8).

Besides the directives, there are also non-binding Guidance documents like MEDDEVs, consensus statements and interpretative documents that ensure uniform application of the relevant provisions of the directives within the EU.

MEDDEVs have the objective of put forward a common approach by MDs manufacturers and NBs involved in the conformity assessment procedures, and by CAs charged with safeguarding Public Health. These guidelines are the result of a consultation process with all the stakeholders, and result from the reflected positions of representatives of CAs and Commission Services, NBs, industry and other interested parties in the MDs sector (24).

1.3.8. New European regulatory proposals

The current MDs and IDVs are increasingly sophisticated and innovative but the current legislation has not kept pace with technical and scientific progress. The great diversity and innovation capacity in this sector has been a challenge to the regulation of these innovative products, specifically by seeking clinical evidence that support their safety and performance. Hence, European Commission adopted in 2012 a package on innovation in health, consisting of adapting the MD legislation to the needs of tomorrow with the aim of achieving a suitable, robust, transparent and sustainable regulatory framework.

The new regulatory framework of MDs proposed by European Commission consists of two proposals for regulations, one is applicable to IVDs and another is applicable to the other MDs (including the implantable active medical devices).

Major goals of these regulation revisions include improving harmonization between Member States (since the application of the existing MDs directives is different across the EU) and reinforcing the safety and health of patients, while still ensuring prompt access to innovative devices for patients and medical professionals.

The main elements of the proposal regulations are:

- The directives will be replaced by regulations. So they will have direct effect in Member States allowing for a better harmonization in the European market;
- Cover legislation gaps. Currently there are regulatory gaps or uncertainties with regard to certain products such as implants for aesthetic purposes;
- Determine specific requirements for the NBs' designation and create mandatory accreditation standards;
- Develop specific measures for controlling and monitoring the activities performed by NBs.
- NBs shall conduct unannounced audits of manufacturers to evaluate their compliance with the legal obligations;
- Clarify the rights and responsibilities of all market players of MDs including the manufacturers, importers and distributors;
- Create a public database of MDs at European level accessible to all, including not only health care professionals but also patients;
- Adapt the rules to technological and scientific progress, for example, adapt the requirements of safety and performance to new health technologies, such as software or nonmaterial used in health care;
- The creation of a new expert group (the Medical Device Coordination Group). It will have the power to review and comment on NB assessments of high-risk MDs before the MD is put on the market.
- Create a unique identification system for MDs that ensures their traceability throughout all the distribution chain;
- Introduction of the new concept of "qualified person". A person responsible for regulatory compliance;
- New rules for the reprocessing of single-use MDs if the reprocessors take on the responsibilities of the manufacturer;

- Establish new requirements for clinical trials to ensure safety of patients and users;
- Provide better coordination between NCA to ensure that only the safe MDs are available on the European market (16, 25).

2. On- the-Job Training

During my internship at DPS I had the opportunity to perform tasks of technical of market surveillance, more specifically directed to the market of the Portuguese manufacturers. I collaborated in the validation/evaluation processes of MDs registered in an online platform directed to manufacturers/authorized representatives, named FABDM. In addition, I did the issuance of certificates of free sale, evaluated MDs as part of a campaign, replied to requests for information and collaborated in the development of a COEN.

Along this period I also had the opportunity to contact with other areas, including quality and surveillance of MDs. However, I did not work directly in these areas, so I will later only make a brief reference to them.

In compliance with INFARMED's quality policy and to comply with the quality system, I was instructed to follow the established procedures and comply with the quality manual. Additionally I had the chance to attend an internal audit that gave me a more accurate view of the quality management system.

2.1. Information requests

During the first weeks, and after being aware of the principal MDs' legislation and guidelines, I began to reply to information requests received by DPS via email. The majority of the requests were related to the MDs' regulatory framework including their qualification and classification. I also requested to duties of manufacturers/ authorised representatives and distributors in the registry of MDs and patient/ heath care professionals' doubts and concerns about the MDs.

The replies to questions about qualification and classification usually included the definition of MD according to the Directive 93/42/EEC and the reference to the guideline MEDDEV 2.4 – Classification of MDs.

In case of requests related to the registry of distributors and manufacturers/authorized representatives, the companies were informed that according to Decree-Law 145/2009 of the 17th of June that transposes to our national law the Council Directive 93/42/EEC of 14th of June, who places the MDs on Portuguese market, must notify INFARMED. While manufacturer, when MDs of class IIa, IIb and III and implantable active MDs, are placed on

the Portuguese market, the manufacturer or the authorized representative needs to notify them in INFARMED, according to the Article 11 of the Decree-Law 145/2009 of the 17th of June that transposes Article 14 of Council Directive 93/42/EEC of 14th of June. For class I MD, systems and sets (i.e. particular medical procedures consisting of various medical devices that are packed and dispensed jointly as a single unit, and are placed on the market under a single trade name [26]) and custom made MD, national manufacturers or his authorized representative based in Portugal shall do their registry. The notification must be carried out in the online notification system for the manufacturers available in INFARMED's website.

On the other hand the distributor of the MDs in Portugal (class I, IIa, IIb, III and implantable active medical devices),must carry out the notification of the devices as well, according to the Article 41 of the above mentioned Decree-Law in the online notification system for distributors. The distributor registry is a legal obligation specifically required by the Portuguese Legislation. The MDD does not address this registry. However, Portugal adopted this system in order to have a better knowledge of the MDs market in our territory.

The registers performed by the manufacturer and the distributor are independent of each other and they are updated in two different databases.

In order to reply patients' requests regarding the safety and conformity of the MDs, I checked if the MD was registered on FABDM or SDIV. If the register was not performed, it was necessary to contact the distributor or the manufacturer in order to apply for registration and then proceed to the formal evaluation of the MD. After this, and according to each specific situation, it was possible to reply to the patients.

2.2. DMs' Evaluation

As previously referred, MDs need to bear a CE mark to be placed in the market. The exceptions are the custom-made devices (i.e. a MD specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient [26]) and devices intended for clinical investigation that need to comply with the provisions of Annex VIII of MDD regarding the statement on devices for special purposes (27).

For class I devices, the manufacturer/ authorised representative is the only responsible for placing the CE mark. He shall elaborate the declaration of conformity and notify the CA.

For classes IIa, IIb, III, in the case of products placed on the market in a sterile condition and with a measuring function it is necessary the intervention of NB. In this case, it is the NB that issues a certificate of conformity according to the conformity assessment procedure chosen by the manufacturer.

Table 3 –Conformity assessment procedures (14)

Classes	Evaluation procedures- Annexes
Class I	VII
Class I sterile and with measuring function medical devices	VII + IV, or V, or VI or II (excluding section 4)
Class IIa	VII + IV, or V, or VI or II (excluding section 4)
Class IIb	III + IV, or V, or VI or II (excluding section 4)
Class III	III + IV, or V or II (including section 4)
Implantable active medical devices	XII + XIII or XIV or XI

2.2.1. MD's evaluation- FABDM's platform

INFARMED uses the FABDM platform to perform the formal MDs' evaluation. Following the implementation of the Medical Device Repository, it was considered appropriate to develop a database that allows the MD's registry as per the applicable legislation. So, in 2012 the on-line registration for MDs/IVDs by its Manufacturers/Authorized Representatives (FABDM) was

launched and came to replace the previous registration procedures. This platform allows consulting the conformity documentation attached and sending the requests of elements directly to the manufacturer.

In the FABDM, the register of Class I MDs, Class I sterile and MDs with measuring function, DIVs, MD systems and sets generates a task of the respective MD automatically. However, for Class IIa, Class IIb, Class III and Implantable active MDs the tasks are not generated automatically, they are created by own manager. This type of evaluation is named ad-hoc evaluation and usually it appears in the context of other procedures / surveillance actions, such as certificate requests.

I performed the evaluation of different types of MDs through the FABDM platform as process manager. The medical device systems and sets (MDSS) for collecting stem cells during delivery and sets for first aids were the first type of processes that I managed. The evaluation of these MDSS presupposes the individual evaluation of the MDs that are part of the set. This includes the evaluation of labeling and instructions for use. In MDDS, the CE marking is not affixed to the packaging of the set but is affixed individually to each device. Additionally, during the evaluation, it is necessary to check the data inserted in the platform such as manufacturer's data, MD's name, MD's reference, NB and Global Medical Device Nomenclature (GMDN is an international system of terms applied to MD for their identification) code and the description and intended purpose of the MD. In case that supplementary information is required, an element request was sent directly to the MD's responsible. After collecting the required information, the final evaluation by process manager is performed and then a message is generated for the final approval by the technical direction. The MD's status is updated after superior approval (validated) (28).

After finishing the evaluation of the MDSS, I started the evaluation of the MDs of class I and II, more specifically, MDs of the type of bandages, compresses, and chirurgical instruments. The major difference between the formal evaluation of class I and class II devices is the fact that the essential requirements of class I MDs need to be analyzed and for Class II it is not necessary because class II MDs are already evaluated by NBs. The analysis of the essential requirements includes the confirmation of adequacy of the standards and specifications used by manufacturer to the type of MDs and if they are the most current ones. There are thirteen essential requirements subdivided into several points and described in the annex I of MDD. Manufacturers need to specifically refer to each requirement are applying and indicate their applicability or not. Whenever applicable, they have to refer which standard or procedure was used to ensure compliance with this requirement (16). The standards that cover the essential requirements of the MDD are published in the Official Journal of the European Community (29).

The evaluation of the label and user instructions is made according to the set out in the MDD and in the MDs' Portuguese law. Furthermore, the manufacturers upload the CE certificate and the DoC in the field "associated documentation" and they must also be analyzed during the MD evaluation.

2.2.2. SDIV's platform

As mentioned above, the Decree-Law 145/2009 of the 17th of June and Decree-Law 189/2000 of the 12twof August determine the obligation of distributor to registry the MD placed on the market. This allows the INFARMED to gain knowledge about the MDs placed in the market and the economic agents involved in the supply chain.

In this platform, the distributor must include mandatory information as the complete identification of Manufacturer/ Authorized Representative, a detailed product description, designation of the product, GMDN code or, alternatively, a brief description of the MD and the purpose of its use, brand and model, class of risk, and NB's code (if applicable).

Validation of the information contained in the register is triggered by different processes, in a proactive way when the procedures are carried out in the context of campaigns or within the context of the codification. Alternatively, validation may be triggered in a reactive way when the certificate was requested to attest the registration of the products or any other surveillance action of MD's market.

My experience with SDIV boils down to specific situations concerning requests for information and within the campaign I attended (30).

2.3. Campaigns

Campaign process is a mechanism by which the DPS and the Directions of Proof of Quality and/or Licensing and Inspection perform an action to a specific group of DMs. The DPS collaborates in the campaigns by performing the documental evaluation and verifying the compliance with the essential requirements according to the MD´s legislation.

Within this type of processes I performed the evaluation of the labels and instructions for use of MDs' disinfectants. Commonly, disinfectants are classified according to rule number 15 of the MD's classification. Disinfectants intended to be used for disinfecting MDs are classified, in general, as Class IIa, unless they are specifically designed to disinfect invasive MDs. In this case they are classified as Class IIb. Once these devices are classified as Class IIa or Class IIb, a NB is

required to assess the technical documentation. Due to this, during the evaluation process of labeling, it is of major importance to check if the CE mark includes a NB's number (Figure 5) (21).

Figure 5 – Shown is the CE mark and NB's number (31)

To perform the assessment of these MDs, I also used to verify if the symbols affixed were according to the standard ISO 15223-1:2012 (32).

2.4. Compliance and Enforcement Group (COEN) and Enquiry CA related to regulatory status and questions of classification.

Throughout the MDs' evaluation, some doubts/questions about regulatory issues such as qualification and classification or even non-compliances may appear. Hence, in some cases it is necessary to contact other CAs to clarify these issues. In case that the issue is specific to a DM/manufacturer, it is triggered a COEN. The COEN is a process developed at European level that allows the CAs to contact manufacturers responsible for DMs in European Community in a faster and more objective way. For this purpose, it is used a common document named COEN2 that harmonises the communications between the CAs requiring their cooperation on the market surveillance (33).

The Enquiry to MD CAs is another request used by CAs to determine borderline or classification issues. The applicant sends to other CAs a form that should include a summary (description of the problem), the question and all pertinent information (e.g. the scientific references and guidelines). The answer may be positive, negative or new proposal. The CAs shall respond providing a rationale with their opinion. The final assessment is carried out in the working party on borderline and classification after establishing a proposal text to be included in the manual on borderline and classification.

During my internship I only had the opportunity to help to prepare a COEN concerning to custom-made MD. I did not prepare any Enquiry to MD CA but I had the opportunity to see several ones.

2.5. Certificate of Free Sale (CFS) for Medical Devices and Certificate Manufacturer / Distributor

For products that are exported outside of the EEA, the CAs of the receptor countries that recognize the European Legislation request a proof of compliance with the current legislation of the origin Country. The main purpose of the CFS is the liberation of the products when exported for third countries. Usually, the certificates are valid for one year, but in exceptional duly justified cases it can go up to 3 years validity.

In order to give a certificate, it is necessary that the applicant: 1) is registered as manufacturer at INFARMED; 2) has all the fees paid; and 3) the device(s) in question must be validated (meeting all compliance requirements stated in MDD)(34).

The Certificate Manufacturer/Distributor certifies that the manufacturer or distributor, respectively, comply with the registration requirement of MDs (according to the Article 11 for manufacturers and article 41 for distributors of the Decree-Law 145/2009 of the 17th of June) and the information provided in the context of MDs' registers is validated by INFARMED (35).

Along the internship I performed one CFS. In such case, I had to do a previous validation of the MD because it was registered but not validated yet.

2.6. Medical Devices Vigilance

Although I did not perform vigilance tasks as part of the DPS, I contacted with this area and I learnt some fundamental concepts.

Post-market surveillance and vigilance is a legal obligation of the manufacturer as established in MD legislation to ensure the continued safety and performance of devices in use. It is also important to minimize the risks in warning situations through effective communication and recall of products if necessary.

INFARMED is the responsible for the National Vigilance System of MD, that aims to collect information concerning MD use and do their evaluation and, ultimately, take appropriate measures to ensure the safety and welfare of citizens, if necessary (36).

The manufacturers, authorized representatives, distributors, health care professionals and other MD's stakeholders, as stated in article 27 of the Decree-Law 145/2009 of the 17th of June, should communicate to the CA all incidents that occur in Portugal. The report should be made by completing the respective form available in INFARMED website and send it by email to the Vigilance Unit of health products (37).

3. Discussion

Many of the requests for information that I answered were related to the issues of classification / qualification of DMs. Although the existing rules adequately classify the vast majority of existing devices, the classification of a small number of products is not so straightforward. Such cases include those devices that are borderline cases between two different classes of MDs. In these particular cases the risk classification may be not adequate to these MDs and these situations could result in a wrong level of conformity assessment in the light of the hazard represented by the device (38). Furthermore, in my opinion the issues of classification/qualification arise also due to the difficult interpretation of the legislation.

Specifically, two of the total requests for information that I had in my charge were borderline cases. One was about eye drops and the other was about insect repellent. Several of eyes' drops are qualified as MDs but this qualification is not always consensual, and so in the borderline manual this issue is already included. The problem with the qualification of this eye drop is the intended purpose and its mode of action. The manufacturer classified its product as Class II for treatment of dry eye or ocular discomfort including contact lens wearers. As the manufacturer does not exclude non users of contact lenses, the purpose of this eye drop is not specifically hydrating of the contact lenses. So, the issue about the correct qualification of this product is raised and the rule 15 of Annex IX of MDD is excluded. Besides this, the manufacturer indicates an anti-inflammatory action that raises another issue: the mode of action. Eye drops whose principal mode of action is pharmacological, immunological or metabolic will fall under the definition of a medicinal product. In order to clarify these issues I asked for some clarifications, however I don´t know the conclusion of this process because when I finished my internship the process was still ongoing. Nevertheless, I think that after clarifying the mode of action, the product may be classified as class IIa or class IIb, in accordance with classification rule 5 or qualified as medicinal product (14, 27, 39).

Through an information request, I received another borderline case about insect repellent. In this case, the manufacturer asked directly how he could qualify the product. He specified that his product was a repellent bracelet against malaria-bearing mosquitoes to prevent malaria. At a first instance, it seems that this product fits with one of DM's purpose according to MDD, "prevention of disease", but it is not true. Actually the primary purpose of this product is repelling Anopheles mosquitoes and their bites. So, according to Annex V of Directive 98/8/EC, this product is considered a biocide (39, 40).

During the evaluation of the disinfectants, in the framework of the campaign, the borderline qualification was again raised. Usually the common disinfectants for disinfection of various surfaces as floors and sanitary facilities are regulated within the biocides legal framework.

According to the purpose for use, disinfectants may be regulated as MDs, medicines or biocides. In some of the labels of the disinfectants that I evaluated, it is stated that the product is for multiple purposes including disinfection of surfaces, walls, countertops and also for surgical instruments. In these cases, these products should not be covered by MDD, however the manufacturers include them within this directive. Only disinfectants whose main purpose is disinfection of MDs can be qualified as MDs (39, 41). Moreover, some of these disinfectants had faults/defaults in their labels and instructions for use. More commonly, labels and instructions for use are not translated to Portuguese, it is used outdated symbols and even the instructions for use are absent. All of these issues were collected and recorded to take the suitable measures in the course of the campaign.

Besides these specific cases, many other issues/doubts on MDs' qualification and classification occur very often. For instance, similar products that are intended to be ingested can be qualified as medicine, MD or food supplement. This issue needs to be clarified for keeping the safety of the patient and have a consistent rule across the EU. The issue about classification/qualification is already provided in new proposed Regulations on MDs and on IVDs.

In general, the principal problems I found during the evaluation of MDs were:

- Error in the GMDN code or outdated code
- Lack of t instructions for use or labeling
- Non-compliant labeling
- The labeling and/or instructions for use are not in national language (Portuguese)
- MDs without DoC and/or EC Certificate
- Outdated standards
- Lack of clinical evaluation

Most of these problems are solved easily with an order of elements such as the correction of the GMDN and updating of the standards. Regarding to labeling and instructions for use, the main problems detected were symbols that were not in accordance with ISO standard 15223-1: 2012 and the absence of mandatory elements such as address of the manufacturer, storage conditions and indication of instruction for use. Often the manufacturers justify the lack of information as a consequence of the insufficient space in labeling. Another common problem is the labeling and instructions for use that are not presented in Portuguese. Many Portuguese distributors complain

to the difficulty in obtaining labels and the instructions for use in Portuguese by manufacturers. As the MDs market for Portugal is small the abroad manufacturers do not want to make large investments including performing the translations.

Another issue that sometimes happens is the absence of clinical evaluation data. This is because many of the Portuguese manufacturers are manufactures of the simpler devices of low classes. In most cases, this issue is solved by the fact that the products are in the market for several years (well established use) and, thus, are able to make an assessment based on the review and compilation of published clinical experience. Nevertheless, often, manufacturers have difficulties in finding scientific literature of MDs that are equivalent to their devices.

Generally and given the current paradigm of the market for MDs and following the scandal with "Poly Implant Prothèse" (PIP) it is clear the need to implement the planned measures foreseen in new regulation proposal. The EC and EU countries have taken joint action to increase control of the MDs based on current legislation, the so-called PIP Action Plan. The principal areas of action of this plan are: functioning of NB, market surveillance, coordination between Member states in fields of vigilance, communication and transparency.

The goal of the new Regulations is a tightening up of the regulatory framework, maintaining the CE mark system and not performing a complete revision. It is necessary to ensure quality, public safety and financial sustainability while it is guaranteed the access to innovative medical technology. For manufacturers, the new regulation will impose some additional burdens mainly for the small and medium-size enterprises (25). Hence, for manufacturers, particularly for Portuguese manufacturers, these measures will require a greater effort of adaptation, more resources and investment. It is also my opinion that this new proposal is essential to ensure the high level of safety patient and health professionals and restore their confidence in the MDs and simultaneously keep MDs' European competitiveness in the global context. Nevertheless, I believe that many of these measures will be a new handicap to the manufacturers in particular for Portuguese manufacturers that are typically small enterprises. On the other hand, it is created the perfect time for the modernization of these enterprises. One should bet on the integration of knowledge coming from the academies, investing more in research applicable to the industry context (42).

Given the current technological and scientific development, not only companies need to help and cooperate with the academies but also the other stakeholders, such as the CAs and NBs need the cooperation of experts in different areas of technological development. According to this, the new proposal also establishes the existence of an expert group to advise and provide assistance (43).

In Portugal, in line with some of the proposed measures to the new regulatory framework, besides the mandatory registration for manufacturers, distributors also have an obligation to register MDs distributed by them. This measure is often contested by distributors because in their opinion the register by all distributors is an unnecessary obligation when one of them did a previous register of the same MD. Nonetheless, the goal of this measure is to allow for a greater control and traceability of MDs that are in the Portuguese market and know all the economic operators associated to a specific MD. This matter would be overcome if the registration of MDs would be single and centralized (43). The assessment of the MD would be carried out by a reference member state just like in the evaluation of medicinal products in the process of mutual recognition or decentralized procedures. The evaluation of each MD would be done once in a single moment and would be valid for other member states. This would decrease the administrative burden of the member states and manufacturers / distributors / importers of MDs would only have to notify their products once they were in the European market. By examining the distribution platform SDIV and comparing it with the register performed in manufacturer platform FABDM, we can see that many foreign manufacturers have their products in the Portuguese market but it is not registered in FABDM. With the single register this infringement would cease to exist. This issue will be solved with the future Eudamed. It is a database in which it will be expected a single record by the manufacturer, distributor and importer valid throughout Europe. Besides the MDs' identification and the economic operators' identification, the Eudamed III will include certificates, vigilance information, clinical investigation and market surveillance (44, 45).

Portugal also developed a system for recording and coding devices that allows the tracking and identification of the devices used in public hospitals. The encoding process is intended to allow characterizing the national market in terms of volume of use and expense value. This is a step towards the need to create a unique device identification system for MDs as included in the new proposal. The encoding should be in a worldwide level to ensure the proper traceability of the MDs (10, 43).

Despite the fears and uncertainties of the new proposal, it is obvious to all stakeholders that the new proposal must be implemented. Until then, it is predictable that many changes and corrections will occur, since the new legislative framework is still under construction. Along with that, MD companies and regulators have to adapt to meet these new measures.

4. Conclusion

The opportunity to do the internship at INFARMED surpassed the expectations that I had. This experience was the catapult that I needed to move to a new area of work and achieve my professional goals. Despite being a curricular internship, this was not my first professional experience. Previously, I had worked as a pharmacist for four years in a community pharmacy. I had the urge to communicate with customers and sense of responsibility. However, I felt like a rookie because I found myself in an area that I was totally unaware: MDs and regulation. Although I had worked in a pharmacy and I had contacted and sold MDs, I did not know much about this subject. The first concepts about MDs were given to me during the Master's Degree in Pharmaceutical Medicine.

I consider that the main transversal skills that I acquired during the internship were the interpretation of regulatory documents and the formal communication in the professional context. Moreover today I consider fruitful to have the regulator-side vision.

The major goals proposed for the internship were achieved. However I would like to have had more contact with the Vigilance Unit because I have interests in this area and in my current work I need to deal with MDs' vigilance. Therefore, this experience would have been an added value for my professional needs.

As a pharmacist I was curious to know another department that works with medicines. So, the opportunity to pass through the DAM and contact with a different but complementary area was grateful and a privilege.

I believe that the traineeship is of utmost importance to the integration and consolidation of the theoretical knowledge acquired during the Masters. On the other hand, the knowledge acquired during the Master's program gave me the skills to successfully finish the training.

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